BMJ Open

Effect of methylene blue on outcomes in patients with distributive shock: a meta-analysis of randomised controlled trials

Xinhui Huang [1,2], Wenqing Yan [3], Zhi Chen [4], Yihong Qian[2]

To cite: Huang X, Yan W, Chen Z, *et al*. Effect of methylene blue on outcomes in patients with distributive shock: a meta-analysis of randomised controlled trials. *BMJ Open* 2024;**14**:e080065. doi:10.1136/bmjopen-2023-080065

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-080065).

Received 20 September 2023
Accepted 20 December 2023

[1]Medical College of Nanchang University, Nanchang, Jiangxi, China
[2]Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi, China
[3]Tongji Hospital, School of Medicine, Tongji University, Shanghai, China
[4]Department of Critical Care Medicine, Tongji Hospital, School of Medicine, Tongji University, Shanghai, China

Correspondence to
Yihong Qian;
155283236@qq.com

ABSTRACT

Objective This meta-analysis aimed to demonstrate the effect of methylene blue (MB) in patients with distributive shock.

Design Meta-analysis.

Methods According to the Prospective International Register of Systematic Reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we searched the relevant randomised controlled trials (RCTs) via PubMed, Embase and Cochrane Library from the date of database inception to 19 April 2023. The primary outcome was mortality during follow-up, and secondary outcomes included mean arterial pressure (mm Hg), mechanical ventilation time (hours), intensive care unit (ICU) length of stay (LOS) (days), hospital LOS (days) and heart rate (times/min).

Results This study included six RCTs with 265 participants. The study showed no significant difference in mortality between the MB and placebo groups (ORs: 0.59; 95% CI 0.32 to −1.06). However, MB reduced the duration of mechanical ventilation (mean difference (MD): −0.68; 95% CI −1.23 to −0.14), ICU LOS (MD: −1.54; 95% CI −2.61 to −0.48) and hospital LOS (MD: −1.97; 95% CI −3.92 to −0.11).

Conclusions The use of MB may not reduce mortality in patients with distributive shock, but may shorten the duration of mechanical ventilation, ICU LOS and hospital LOS. More clinical studies are needed to confirm these findings in the future.

Trial registration number CRD42023415938.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study discussed the effect of methylene blue in distributive shock based on different settings and patient types.
⇒ The trial sequential analysis was used to test the stability of the results of this meta-analysis.
⇒ The heterogeneity of the combined studies was low.
⇒ Due to the limited sample size and the use of vasoactive drugs, the findings of the study should be cautiously interpreted.

BACKGROUND

Distributive shock is the most common shock encountered in the intensive care unit (ICU).[1 2] Distributive shock occurs in 63% of patients with shock in the ICU.[1] Causes of distributive shock include septic shock, surgery, systemic inflammatory reactions and allergic reactions.[3] Distributive shock is caused by the inappropriate activation of vasodilatory mechanisms and failure of vasoconstrictor mechanisms.[4] Vasoactive drugs are one of the most important means in the treatment of distributive shock.[5] Given the mechanism of distributive shock, high doses of vasoactive drugs may be required to achieve haemodynamic goals. However, this may increase the risk of adverse events, such as arrhythmia, tissue ischaemia, necrosis and immune dysfunction.[5] Recently, there has been a search for more effective treatment options to improve clinical outcomes.

Methylene blue (MB) is considered the first synthetic drug to be used in humans and has been used for a variety of clinical indications, including vasoplegic shock.[6] Vasoplegic shock, synonymous with distributive shock, is a more prominent circulatory imbalance with tissue hypoperfusion.[7] Some studies[6 8] have shown that induced nitric oxide synthase-NO-soluble guanosine cyclase-cyclic guanosine monophosphate (iNOS-NO-sGC-cGMP), signal transduction pathway plays an important role in the pathogenesis of septic shock. As an inhibitor of sGC, MB can effectively block the signal transduction pathway, remove excessive NO and inhibit iNOS, reduce the production and activity of NO, inhibit the effect of cGMP, and improve patients' hypovolaemic state by constricting blood vessels. However, the efficacy of MB in patients with distributive shock remains controversial. In 2022, a meta-analysis containing 15 studies indicated that[9] compared with placebo, MB reduced mortality in patients with distributive shock but had no effect on the duration of mechanical ventilation, ICU length of stay (LOS) or hospital LOS. A recent randomised controlled trial (RCT) including 91 patients with septic shock showed that[10] MB may shorten ICU LOS and hospital LOS but not

Table 1 Study characteristics

First author	Publication year	Sample size (n)	Age, mean years (SD)	Diagnosis	Severity of illness (I/C)	Types of vasoactive drugs	Dose (mg/kg)	Mortality follow-up period (days)
Kirov	2001	20	MB: 55.3 (20.9) C: 59.4 (14.5)	Septic shock	SOFA MB: 10.1 (2.1) C:10.5 (3.7)	1, 2, 3, 4	MB: 2 mg/kg (intravenous)+0.25–2.00 mg/kg/hour (intravenous 4 hours) C: placebo	28
Koelzow	2002	38	MB: 48.1 (2.7) C: 46.8 (3.6)	Ischaemia reperfusion syndrome	N	2, 3	MB: 1.5 mg/kg (intravenous) C: placebo	30
Memis	2002	30	MB: 53.13 (18.33) C: 51.73 (14.49)	Septic shock	SOFA MB: 6.2 (3.3) C: 7.06 (5.17)	N	MB: 0.5 mg/kg/hour (intravenous 6 hours) C: placebo	28
Levin	2004	56	MB: 60.6 C: 59.2	Vasoplegic syndrome	N	4	MB: 1.5 mg/kg/hour (intravenous 1 hour) C: placebo	Perioperative period
Maslow	2006	30	MB: 69.8 (6.6) C: 68.4 (10.6)	Vasoplegic syndrome	N	2, 3, 4, 5	MB: 3 mg/kg (intravenous) C: placebo	CPB period
Ibarra-Estrada	2023	91	MB: 46 (12.25) C: 45.94 (22.19)	Septic shock	SOFA MB: 10 (3.06) C: 10 (3.01)	4	MB: 1.2 mg/kg (intravenous)+100 mg/day (intravenous 6 hours) C: placebo	28

Types of vasoactive drugs: 1, dobutamine; 2, dopamine; 3, epinephrine; 4, norepinephrine; 5, phenylephrine.
C, placebo; CPB, cardiopulmonary bypass; MB, methylene blue; N, not mentioned in the article; SOFA, Sequential Organ Failure Assessment.

reduce mortality in patients. Currently, it is necessary to update the results of the meta-analysis. Therefore, we conducted a meta-analysis of patients with distributive shock treated with MB and tested the stability of the results using the trial sequential analysis (TSA).

METHODS

Retrieval strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] Two authors (XHH and WQY) searched for relevant RCTs published in the PubMed, Embase and Cochrane Library databases, and the search time was from database establishment to 19 April 2023 (online supplemental additional file 1). At the same time, the two authors also tried to retrieve relevant studies from other sources (journals, article references). The keywords searched were "methylene blue" and "shock" or "vasoplegia". If the title and abstract could not determine compliance with the selected criteria, the full text was obtained for comprehensive assessment. Articles that met the inclusion criteria were assessed separately by two authors, and those with disagreement on study selection were finally decided by the third author (Y-HQ).

Inclusion criteria

Studies were selected according to the Population, Intervention, Comparison and Outcomes criteria: (1) participants: adult patients (≥18 years old) with distributive shock; (2) interventions: intravenous or continuous infusion of MB; (3) comparisons: intravenous or continuous infusion of placebo; (4) reported at least one of the following outcomes: mortality during follow-up, mean arterial pressure, duration of mechanical ventilation, ICU LOS, hospital LOS and heart rate; (5) study design: RCTs.

Exclusion criteria

The exclusion criteria for the study were as follows: (1) observational studies, case reports and systematic reviews; (2) non-English literature; (3) study subjects were animals or pregnant and lactating patients; and (4) literature with lack of any outcome data.

Data extraction and quality evaluation

Two authors (XHH and ZC) independently conducted data extraction, using a predefined data extraction form, and bias risk assessment and cross-checked the results. In the event of differences, they were finally resolved by the third author (Y-HQ). The extracted data included the first author, publication year, sample size, population baseline characteristics (age), clinical diagnosis, MB and control rehydration strategy, mortality during follow-up, mechanical ventilation, ICU LOS, hospital LOS and heart rate.

Statistical analysis

We used Review Manager V.5.4 to conduct a meta-analysis. ORs and 95% CIs were used to describe differences between classified variables, and mean difference (MD) and 95% CI were used to describe differences between continuous variables. Heterogeneity between studies was assessed by calculating the I^2 statistic. When $I^2 \leq 50\%$, the fixed effects model was used; otherwise, the random effects model was used. Statistical significance was set at $p<0.05$ for all analyses. To test the stability of the results, we performed a sensitivity analysis of mortality using studies with a low risk of bias.

Outcomes and subgroup analysis of this study

The primary outcome was mortality during the follow-up period, and the secondary outcomes included mean arterial pressure, duration of mechanical ventilation, ICU LOS, hospital LOS and heart rate. A subgroup analysis of mortality was performed according to patient type (septic shock/non-septic shock). The quality of the included studies was assessed using the Cochrane Risk of Bias tool.[12] The aspects of evaluation included selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Two authors (XHH and WQY) assess the risk of bias for each trial, and if there is disagreement, a third author (Y-HQ) ultimately makes the decision. High-risk research was defined as including one or more high-risk areas.

Trial sequential analysis

To minimise type 1 and type 2 errors, we performed a TSA of mortality during follow-up using the TSA software.[13] The overall risk of type I error was set at 5% and efficacy at 80%. Mortality (35.04%) of the control group included in the study and heterogeneity of the pooled study (11%) were used, and the relative risk reduction (13%) was estimated based on the study by Ibarra-Estrada *et al*.[10] We observed whether the cumulative Z-curve crossed the conventional and trial sequential monitoring boundaries.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

After screening 1452 articles, six RCTs[10 14–18] (n=265) were included in the analysis (online supplemental figure S1). We tried to search for relevant studies from other sources (journals, article references) but could not find studies that fit the criteria. Five studies were single-centre studies, and the remaining one was multicentre. The study included patients with septic shock, vasoplegia syndrome after cardiac surgery and ischaemia-reperfusion syndrome due to liver transplantation. Follow-up times included 30 days, 28 days, and perioperative and cardiopulmonary bypass periods. Table 1 lists the characteristics of the included studies.

Risk of bias in studies

Six studies were included in this analysis; three[10 14 16] had a low risk of bias and the remaining three[15 17 18] had a

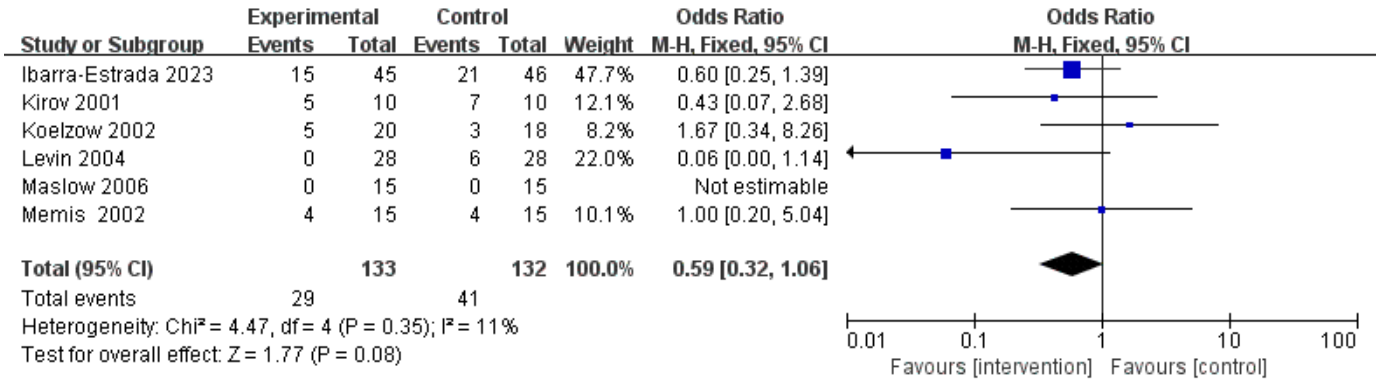

Figure 1 Forest plots of mortality in patients with distributive shock.

moderate risk of bias (online supplemental table S1). The greatest risk of bias originated from selection and detection biases.

Primary outcome: mortality during follow-up

All studies reported mortality during follow-up, with a total of 265 patients. I^2 showed no significant heterogeneity across studies (I^2=0.11); therefore, we used a fixed-effects model. The results showed no significant difference in mortality between the two groups (OR: 0.59; 95% CI 0.32 to 1.06; p=0.08; figure 1).

We evaluated the efficacy of MB using a subgroup analysis based on different disease types. The septic shock subgroup included three studies[10 14 16] with a total of 141 participants. The results showed that compared with the control group, MB did not reduce mortality from septic shock (OR: 0.62; 95% CI 0.31 to 1.25; p=0.19; figure 2). A total of 124 participants were included in the non-septic shock subgroup.[15 17 18] The results showed no significant difference in death rates between the two groups (OR: 0.39; 95% CI 0.01 to 11.62; p=0.59; figure 2). Sensitivity analysis of the primary outcome using a low-risk-of-bias study showed consistent results (OR: 0.63; 95% CI 0.31 to 1.25; p=0.18; online supplemental figure S2).

Trial sequential analysis

The Z-curve did not cross either the conventional boundary or the trial sequential monitoring boundary, and the expected sample size was 2943 cases. This study included 256 cases; therefore, MB did not reduce mortality in patients with distributive shock (figure 3). In the future, more clinical studies are needed to confirm the efficacy of MB.

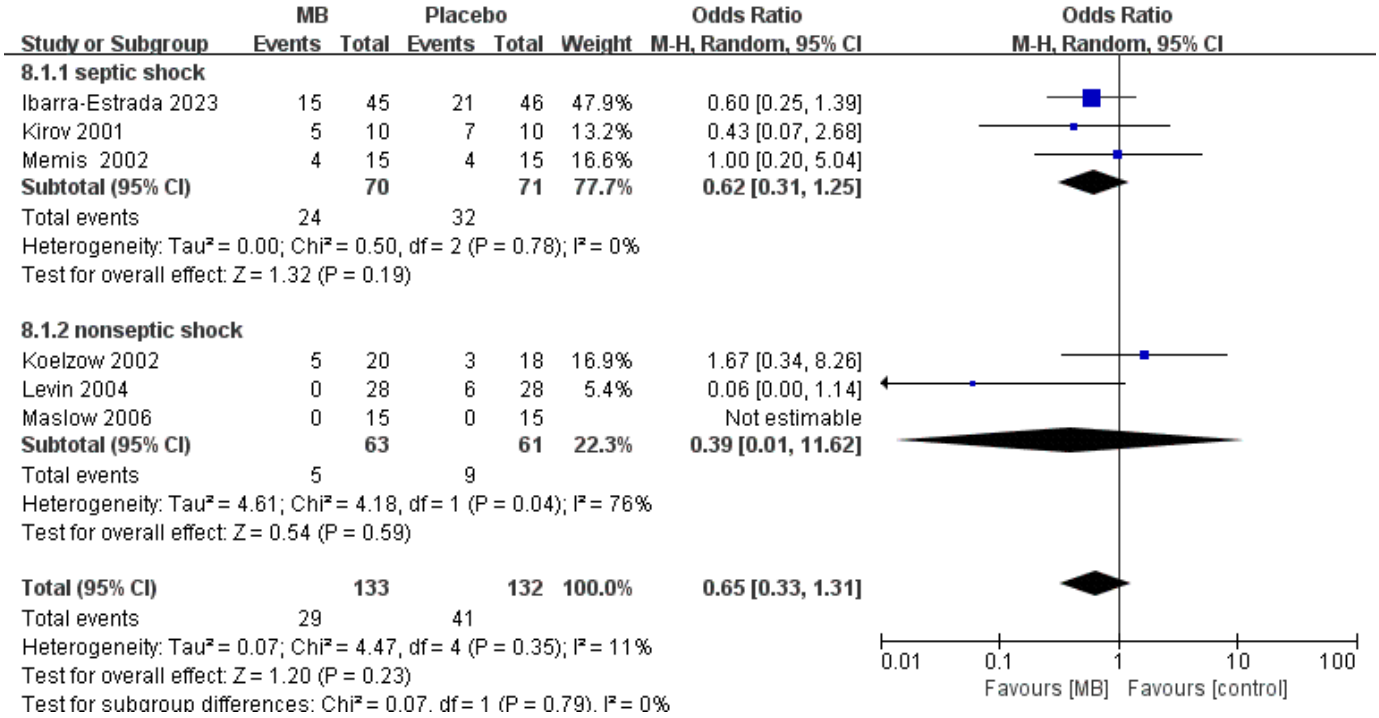

Figure 2 Subgroup analysis of mortality by disease type, comparing intervention and control protocols for distributive shock. MB, methylene blue.

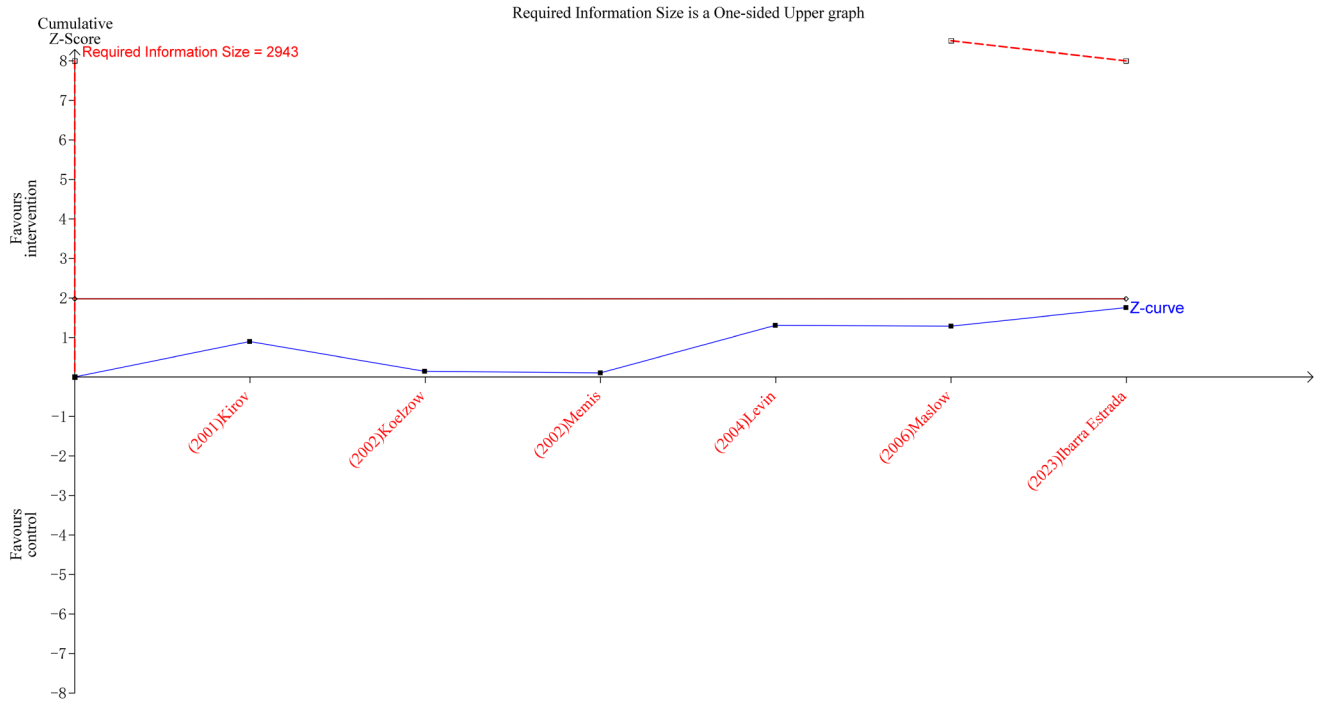

Figure 3 Trial sequence analysis of the effect of methylene blue on the mortality of distributive shock. Trial sequential analysis (TSA) used estimates of 35.04% for baseline mortality, 13% for relative risk reduction, 5% for alpha and 80% for power. The Z-curve in the figure neither crossed the traditional nor the TSA monitoring boundary, and the accumulated amount of information does not reach the expected amount of information.

Secondary outcome: mean arterial pressure (mm Hg), mechanical ventilation time (hours), ICU LOS (days), hospital LOS (days) and heart rate (times/min)

Four studies[14–16 18] reported the mean arterial pressure for a total of 118 participants. The results showed that compared with placebo, MB significantly increased the mean arterial pressure in patients (MD: 6.48; 95% CI 2.65 to 0.27; p=0.01; I^2=41%; table 2).

Three studies[10 14 16] reported the duration of mechanical ventilation in patients. The results showed that compared with placebo, MB reduced the duration of mechanical ventilation during hospitalisation in patients with distributive shock (MD: −0.68; 95% CI −1.23 to −0.14; p=0.01; I^2=0%; online supplemental figure S3).

Three studies[10 14 16] reported the LOS in the ICU. The results showed that MB reduced the ICU LOS in patients with distributive shock (MD: −1.54; 95% CI −2.61 to −0.48; p=0.004; I^2=25%; table 2). Two studies[10 14] reported the hospital LOS, and I^2 showed no significant heterogeneity across studies (I^2=0%). The results showed that MB reduced the hospital LOS in patients with distributive shock (MD: −1.97; 95% CI −3.82 to −0.11; p=0.04; table 2). Comparisons of other outcome measures (eg, heart rate, lactate) are shown in table 2.

Publication bias

A funnel plot test (online supplemental figure S4) was conducted using mortality as an indicator, and the results showed no significant publication bias in any study. We used Eggerr's regression[19] to assess publication bias with consistent results.

Table 2 Data analysis of secondary outcomes

Secondary outcomes	Trials	Sample size	MD	95% CI	I^2 (%)	P value
Mean arterial pressure (mm Hg)	3	118	6.48	2.65 to 0.27	41	0.01*
ICU LOS (days)	3	141	−1.54	−2.61 to 0.48	25	0.004*
Hospital LOS (days)	2	111	−1.97	−3.82 to 0.11	0	0.04*
Heart rate (times/min)	2	50	−1.64	−8.50 to 5.22	34	0.67
Lactate (mmol/L)	3	159	−0.72	−1.33 to 0.12	81	0.02*

*Have statistical difference.
ICU, intensive care unit; LOS, length of stay; MD, mean deviation.

DISCUSSION

This study suggests that MB may shorten the duration of mechanical ventilation, ICU LOS and hospital LOS in patients with distributive shock but may have no effect on mortality. Sensitivity analysis of the main outcome of the low-bias risk study was performed, and the results were consistent with the main conclusions.

MB is a phenothiazine derivative that is inexpensive and easily available and was first applied for staining.[6] In 1976, a study on nephrolithotomy reported the haemodynamic effects of MB.[20] All patients experienced a significant increase in mean arterial pressure after 30 s of MB infusion. MB use for septic shock was first reported in 1992.[21] Two patients with septic shock experienced a significant increase in systemic vascular resistance after intravenous administration of multi-dose MB; however, both patients died of multiple organ failure. Over the past two decades, multiple human studies have been conducted to evaluate the efficacy of MB in treating patients with distributive shock; however, the results have not been entirely consistent.

In 2001, Kirov *et al* conducted the first RCT of MB in patients with septic shock.[14] The intervention group was first infused with 2 mL/kg MB within 15 min. After 2 hours, continuous infusion of MB was done at rates of 0.25, 0.5, 1.5 and 2.5 mL/kg/hour; each infusion time was 1 hour. At the sixth hour of infusion, the mean arterial pressure was significantly higher in the MB group than that at baseline and in the control group. There were no significant differences in mortality (p=0.65), ICU LOS (p=0.69) or hospital LOS (p=0.87) between the two groups. In 2002, Memis *et al* conducted an RCT of 30 patients with septic shock.[16] The intervention group was administered a continuous dose of 0.5 mg/kg/hour MB for 6 hours. At the completion of MB infusion, the mean arterial pressure was significantly higher in the MB group than that at baseline and in the control group. In-hospital mortality was similar between the two groups (26.6%), whereas mechanical ventilation duration (p>0.05) and ICU LOS (p>0.05) were not significantly different. Owing to the difference in disease severity between the patients and the small sample size in both studies, the statistical power to detect significant differences in outcomes was limited. The use of MB resulted in high urine discolouration rates, which may have led to a detection bias in the study.

In 2002, Koelzow *et al* conducted an RCT to observe the effect of MB on ischaemia reperfusion syndrome during orthotopic liver transplantation.[15] The intervention group received 1.5 mg/kg MB. There were no significant differences in mortality (p=0.69) or time to hospital discharge (p=0.78). In 2004, Levin *et al*[17] conducted a study on cardiac postoperative vasoplegia syndrome. Twenty-six patients in the intervention group received 1.5 mg/kg MB. The study showed that compared with placebo, MB reduced patient mortality (p=0.01). In 2018, Habib *et al*[22] conducted a retrospective study on vasoplegia after cardiac surgery. The results suggested that the use of MB could reduce mortality (p=0.04) in patients with postoperative cardiac vasoplegia and shorten ICU LOS (p=0.03). However, owing to the need for surgery, double-blinding could not be achieved in these studies. The use of vasopressors was determined by physicians, and there might have been a performance bias in the study.

In 2022, Zhao *et al* published a meta-analysis of vasodilatory shock.[9] This study demonstrated that compared with placebo, MB reduced mortality in patients with vasodilatory shock (OR=0.43; 95% CI 0.22 to 0.87; p=0.02). However, there was no significant difference in ICU LOS (p=0.16) and hospital LOS (p=0.95) between the two groups. This meta-analysis included observational studies and RCTs; therefore, the quality grade might have been affected. The inclusion of populations, disease severity and interventions was inconsistent, and the post-merger heterogeneity was high, which could have led to potential bias.

In 2023, Pruna *et al* conducted a meta-analysis that included 11 studies.[23] The study showed that MB can improve survival in critically ill and perioperative patients. The results of Pruna *et al* contradict our findings. There are several reasons for this: first, non-English literature was not included in our study; second, our meta-analysis did not include the Ozal *et al* study.[24] In Ozal's study, MB was used as a preventative measure before heart surgery, rather than as a treatment for vascular paraplegic shock. Ozal *et al*'s study had the largest number of participants, which may have a greater impact on the outcome.

Our study included only RCTs to achieve more homogeneity between studies, and we used TSA to improve the validity of evidence. In RCTs, repeated differential testing of the cumulative data expands the overall risk of class I errors; therefore, a restriction is needed in the statistical analysis to determine whether the results are truly statistically significant. TSA was performed to test the stability of the results. According to the TSA results, there was insufficient evidence to support the efficacy of MB in clinical effects, and more clinical studies are needed in the future.

Several limitations should be noted before interpreting the results of this study. First, this study included trials with small samples and may have had publication bias. Second, most trials were single-centre studies, and the results may not apply to all populations. Third, some outcomes such as ICU LOS and hospital LOS were rarely reported, reducing the strength of the pooled studies. Fourth, the use of vasopressors in the trials included in this study was inconsistent, and we could not further determine the influence of these factors on the obtained data. Finally, only English literature is included in this paper, which may cause bias due to language limitations.

CONCLUSIONS

This study suggests that the use of MB in patients with distributive shock may not reduce mortality. However, MB as an auxiliary means can shorten the patient's mechanical ventilation and hospital stay. Owing to the limitations

of the included studies, these outcomes should be interpreted with caution. Future clinical studies with larger sample sizes are needed to determine the effect of MB in patients with distributive shock.

Contributors YHQ designed this study; XHH and WQY searched the database; XHH and ZC designed the tables, and extracted the data; XHH, YHQ and ZC performed statistical analysis; XHH and WQY wrote the original manuscript; YHQ reviewed and improved the manuscript. All authors read and approved the final manuscript; YHQ plays the role of guarantor in this article.

Funding Project supported by the National Natural Science Foundation of China (Grant No. 82160020).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Xinhui Huang http://orcid.org/0009-0009-2744-3702
Wenqing Yan http://orcid.org/0000-0003-3980-0868
Zhi Chen http://orcid.org/0000-0002-9467-9151

REFERENCES

1 Vincent J-L, De Backer D. Circulatory shock. *N Engl J Med* 2013;369:1726–34.
2 De Backer D, Biston P, Devriendt J, *et al*. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779–89.
3 Russell JA, Gordon AC, Williams MD, *et al*. Vasopressor therapy in the intensive care unit. *Semin Respir Crit Care Med* 2021;42:059–77.
4 Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001;345:588–95.
5 Buckley MS, Barletta JF, Smithburger PL, *et al*. Catecholamine vasopressor support sparing strategies in vasodilatory shock. *Pharmacotherapy* 2019;39:382–98.
6 Saha BK, Burns SL. The story of nitric oxide, sepsis and methylene blue: a comprehensive pathophysiologic review. *Am J Med Sci* 2020;360:329–37.
7 Lambden S, Creagh-Brown BC, Hunt J, *et al*. Definitions and pathophysiology of vasoplegic shock. *Crit Care* 2018;22:174.
8 Hosseinian L, Weiner M, Levin MA, *et al*. Methylene blue: magic bullet for vasoplegia *Anesth Analg* 2016;122:194–201.
9 Zhao CC, Zhai YJ, Hu ZJ, *et al*. n.d. Efficacy and safety of methylene blue in patients with vasodilatory shock: a systematic review and meta-analysis. *Front Med*;9.
10 Ibarra-Estrada M, Kattan E, Aguilera-González P, *et al*. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. *Crit Care* 2023;27:110.
11 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
12 Higgins J, Green SR. Cochrane handbook for systematic review of interventions version 5.1.0; 2011.
13 Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;17:39.
14 Kirov MY, Evgenov OV, Evgenov NV, *et al*. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Critical Care Medicine* 2001;29:1860–7.
15 Koelzow H, Gedney JA, Baumann J, *et al*. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. *Anesth Analg* 2002;94:824–9,
16 Memis D, Karamanlioglu B, Yuksel M, *et al*. The influence of methylene blue infusion on cytokine levels during severe sepsis. *Anaesth Intensive Care* 2002;30:755–62.
17 Levin RL, Degrange MA, Bruno GF, *et al*. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg* 2004;77:496–9.
18 Maslow AD, Stearns G, Butala P, *et al*. The hemodynamic effects of methylene blue when administered at the onset of cardiopulmonary bypass. *Anesth Analg* 2006;103:2–8,
19 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
20 Birch AA, Boyce WH. Hypertension and decreased renal blood flow following methylene blue injection. *Anesth Analg* 1976;55:674–6.
21 Schneider F, Lutun P, Hasselmann M, *et al*. Methylene blue increases systemic vascular resistance in human septic shock. *Intensive Care Med* 1992;18:309–11.
22 Habib AM, Elsherbeny AG, Almehizia RA. Methylene blue for vasoplegic syndrome postcardiac surgery. *Indian J Crit Care Med* 2018;22:168–73.
23 Pruna A, Bonaccorso A, Belletti A, *et al*. Methylene blue reduces mortality in critically ill and perioperative patients: a meta-analysis of randomized trials. *J Cardiothorac Vasc Anesth* 2024;38:268–74.
24 Ozal E, Kuralay E, Yildirim V, *et al*. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg* 2005;79:1615–9.

Search strategies

PubMed

1# "Methylene Blue" (Mesh Terms)

2# "Methylene Blue" (All Fields) OR "Blue, Methylene" (All Fields) OR "Methylthioninium Chloride" (All Fields) OR "Methylthionine Chloride" (All Fields)

3# "Shock" (Mesh Terms)

4# "Shock" (All Fields) OR "Circulatory Failure" (All Fields) OR "Failure, Circulatory" (All Fields) OR "Circulatory Collapse" (All Fields)

5# "Vasoplegia" (Mesh Terms)

6# "Vasoplegia" (All Fields) OR "Vasoplegias" (All Fields) OR "Postoperative Vasoplegic Syndrome" (All Fields) OR "Vasoplegic Syndrome" (All Fields)

7# (1# OR 2#) AND (3# OR 4# OR 5 #OR 6#)

Cochrane Library

#1 MeSH descriptor: [Methylene Blue] explode all trees

#2 (Blue, Methylene OR Methylthioninium Chloride OR Methylthionine Chloride):ti,ab,kw

#3 #1 OR #2

#4 MeSH descriptor: [Shock] explode all trees

#5 (Circulatory Failure OR Failure, Circulatory OR Circulatory Collapse):ti,ab,kw

#6 MeSH descriptor: [Vasoplegia] explode all trees

#7 (Vasoplegia OR Vasoplegias OR Postoperative Vasoplegic Syndrome OR Vasoplegic Syndrome):ti,ab,kw

#8 #4 OR #5 OR #6 OR #7

#9 #3 AND #8

Embase

#1 'methylene blue'/exp

#2 'methylene blue' OR 'blue, methylene' OR 'methylthioninium chloride' OR 'methylthionine chloride':ab,kw,ti

#3 #1 OR #2

#4 'shock'/exp

#5 'circulatory failure' OR 'failure, circulatory' OR 'circulatory collapse':ab,kw,ti

#6 'vasoplegia'/exp

#7 'vasoplegia' OR 'vasoplegias' OR 'postoperative vasoplegic syndrome' OR 'vasoplegic syndrome':ab,kw,ti

#8 #4 OR #5 OR #6 OR #7

#9 #3 AND #8

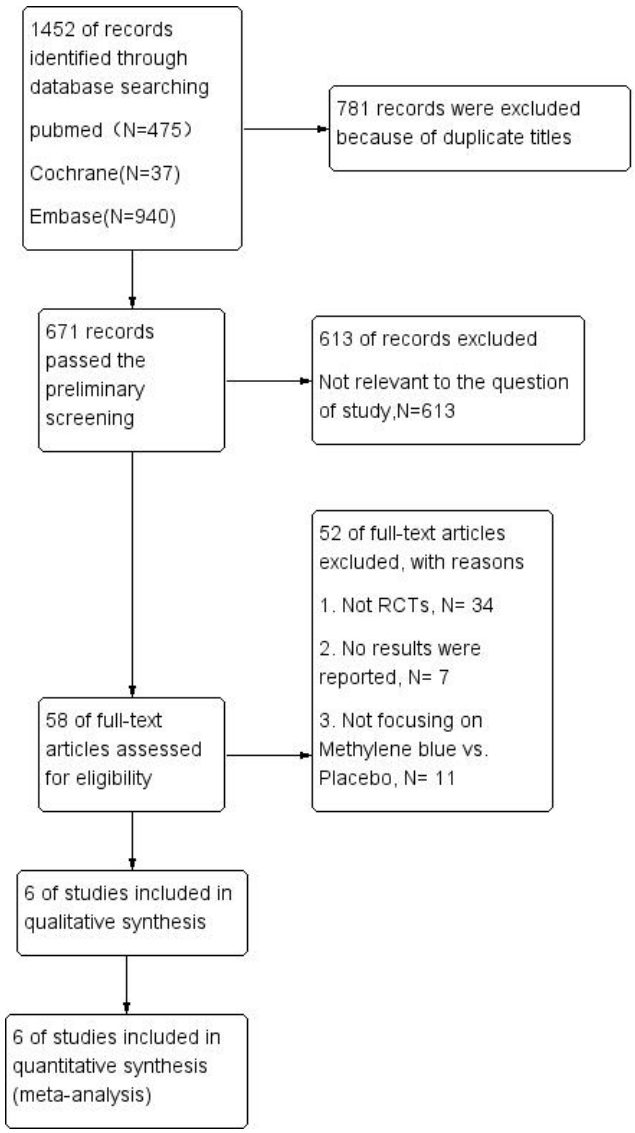

Fig. S1 Study flow diagram.

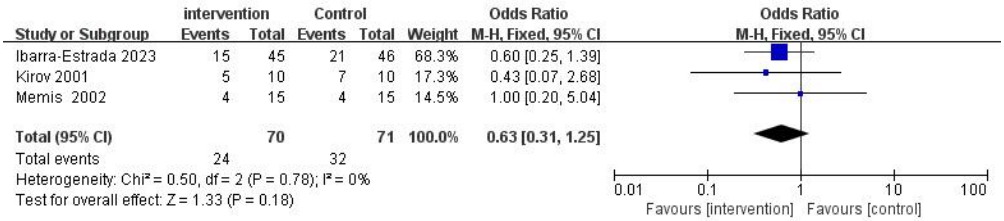

Fig. S2 Sensitivity analysis of mortality in low-bias risk studies.

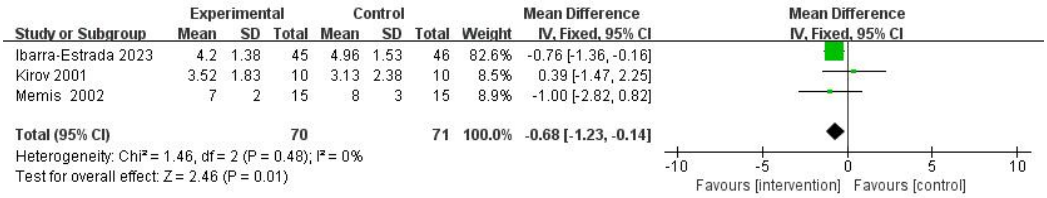

Fig. S3 Forest plots of Mechanical ventilation time in patients with distributive shock.

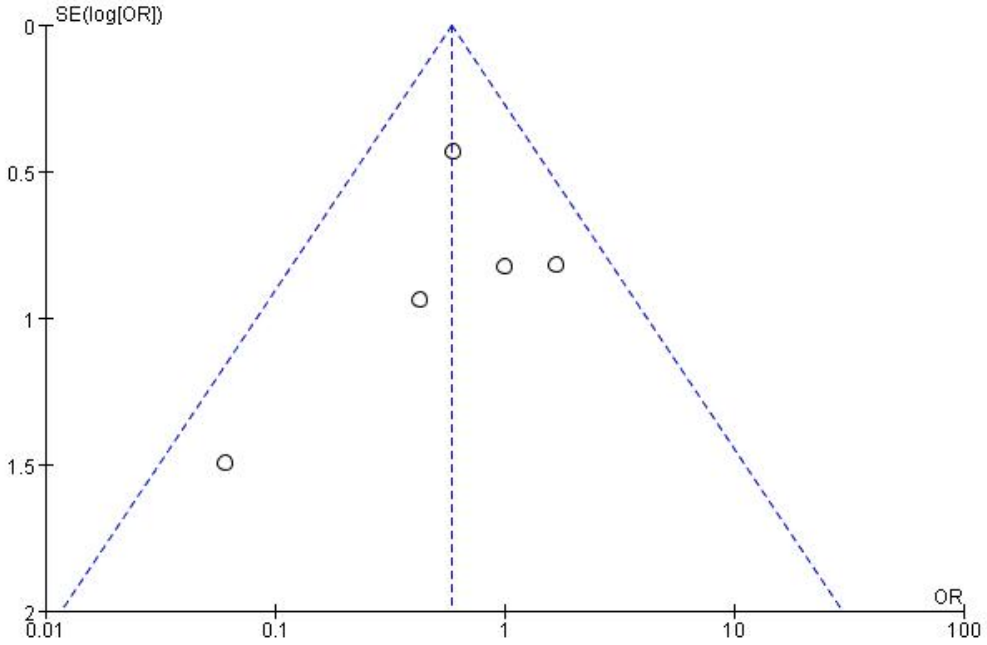

Fig. S4 Funnel plot of mortality during follow-up.

Table S1. Risk of bias

First author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Composite bias
Ibarra-Estrada 2023	+	?	+	+	+	+	+	+
Kirov 2001	?	+	+	+	+	+	+	+
Koelzow 2002	?	?	?	?	?	?	?	?
Levin 2004	?	?	?	?	+	+	+	?
Maslow 2006	?	?	?	?	+	+	+	?
Memis 2002	+	+	+	?	+	+	+	+

"+", low risk of bias; "?", uncertain risk of bias; "-", high risk of bias

Table S2. Data extraction

Study	Address	Diagnosis	Dose(I) (mg/kg)	Sample size	Primary outcome(I/C)		Mean arterial pressure (I/C)(mmHg)		Mechanical ventilation time (I/C)(h)		ICU Length of stay (I/C) (d)		Hospital Length of stay (I/C)(d)		Heart rate(I/C) (times/min)	
Kirov 2001	ICU	Septic shock	2 mg/kg (iv) +0.25–2.00 mg/kg/h (iv 4 h) (N=10)	20	5	7	86.5+13.6	82.5+17.2	84.4+43.9	75.1+57.1	6.4+4	6.1+4.5	17.4+15.5	16.1+15.6	135+27	123+25
Koelzow 2002	Surgery	Ischemia reperfusion syndrome	1.5 mg/kg (iv) (N=20)	38	5	3	80+13.4	69+8.5								
Memis 2002	Anesthesiology	Septic shock	0.5 mg/kg/h (iv 6 h) (N=15)	30	4	4	85+14	74.0+10.3	7+2	8+3	13+2	16+4			112+11	115+9
Levin 2004	Surgery	Vasoplegic syndrome	1.5 mg/kg/h (iv 1h)(N=28)	56	0	6										
Maslow 2006	Surgery	Vasoplegic syndrome	3 mg/kg (iv) (N=15)	30	0	0	60+8	58+8								
Ibarra-Estrada 2023	ICU	Septic shock	100 mg/d (iv 6 h) (N=45)	91	15	21			4.20+1.38	4.96+1.53	6.32+2.14	7.62+3.82	8.15+2.3	10.18+6.05		

I: Intervention group; C: Control group;